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(54) Title: OXAZOLES FOR TREATING CYTOKINE MEDIATED DISEASES (57) Abstract This invention relates to the novel oxazole compounds of Formula (I) and novel pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier. This invention also relates to a method of inhibiting cytokines and the treatment of cytokine mediated diseases, in mammals, thereby by administration of an effective amount of a compound according to Formula (I).		

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Oxazoles for Treating Cytokine Mediated Diseases

FIELD OF THE INVENTION

This invention relates to a novel group of oxazole compounds, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and
10 pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION:

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been
15 demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of
20 prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic
25 inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985), reviews the biological
30 activities which have been attributed to IL-1. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic
35 shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or

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malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg *et al.*, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, *et al.*, Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar reasons as those noted.

Interleukin - 8 (IL-8) is a chemotactic factor first identified and characterized in 1987. IL-8 is produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1, TNF, or lipopolysachharide (LPS). Human IL- 8 has been shown to act on Mouse, Guinea Pig, Rat, and Rabbit Neutrophils. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil

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chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysosomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, this may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutrophils into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production.

IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting cytokines, such as IL-1, IL-6, IL-8 and TNF.

SUMMARY OF THE INVENTION

This invention relates to the novel compounds of Formula (I) and pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

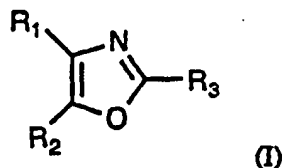
This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

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DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention are represented by the structure:



5 wherein:

R_1 and R_2 are independently selected from an optionally substituted aryl or heteroaryl group, provided that at least one of R_1 and R_2 is an optionally substituted heteroaryl, and further provided that both R_1 and R_2 are not the same heteroaryl group;

10 wherein when one of R_1 and R_2 is an optionally substituted aryl ring, the ring is substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{23}$, $-(CR_{10}R_{20})_m COR_{36}$, $-SR_5$, $-SOR_5$, $-OR_{36}$, halo-substituted- C_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{36}$, $-NR_{10}C(Z)R_{23}$, or $-(CR_{10}R_{20})_m NR_{10}R_{20}$;

15 and which, for other positions of substitution, is halo, $-(CR_{10}R_{20})_m$ -cyano, $-C(Z)NR_{16}R_{26}$, $-C(Z)OR_8$, $-(CR_{10}R_{20})_m$ COR₈, $-(CR_{10}R_{20})_m$ S(O)_mR₈, $-(CR_{10}R_{20})_m$ OR₈, halo-substituted- C_{1-4} alkyl, $-C_{1-4}$ alkyl, $-(CR_{10}R_{20})_m$ NR₁₀C(Z)R₈, $-(CR_{10}R_{20})_m$ NR₁₀S(O)_m R₁₁, $-(CR_{10}R_{20})_m$ NR₁₀S(O)_m NR₇R₁₇, $-(CR_{10}R_{20})_m$ ZC(Z)R₈ or $-(CR_{10}R_{20})_m$ NR₁₆R₂₆;

20 and when one of R_1 and R_2 is an optionally substituted heteroaryl group, the substituent groups include one or two substituents each of which is independently selected from C_{1-4} alkyl, halo, C_{1-4} alkoxy, C_{1-4} alkylthio, NR₁₀R₂₀, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₂₂;

25 R_3 is $-X_aP(Z)(X_bR_{13})_2$, X_c or $-(CR_{10}R_{20})_n R_4$;

R_4 is $Q-(Y_1)_t$;

Q is an aryl or heteroaryl group;

X_c is hydrogen, $-(CR_{10}R_{20})_n (Y_2)_p$, $-(CR_{10}R_{20})_n -C=C- (CR_{10}R_{20})_n (Y_2)_p$,

30 $-(CR_{10}R_{20})_n -C\equiv C- (CR_{10}R_{20})_n (Y_2)_p$, or halosubstituted C_{1-10} alkyl;

t is an integer having a value of 1 to 3;

p is 0 or an integer having a value of 1, provided that when p is 0 then Y_2 is hydrogen;

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- X_a is $-NR_8-$, $-O-$, $-S-$ or a C_{1-10} alkylene chain optionally substituted by C_{1-4} alkyl and optionally interrupted by $-NR_8-$, $-O-$ or $-S-$;
- X_b is independently selected from $-(CR_{10}R_{20})_n$, $-NR_8-$, $-O-$ or $-S-$;
- Z is oxygen or sulfur;
- 5 n is 0 or an integer having a value of 1 to 10;
- n' is an integer having a value of 1 to 10;
- m is 0, or the integer 1 or 2;
- m' is 1 or 2;
- m'' is 0 or an integer having a value of 1 to 5;
- 10 Y_1 is independently selected from hydrogen, C_{1-5} alkyl, halo-substituted C_{1-5} alkyl, halogen, $-X_a-P(Z)-(X_bR_{13})_2$ or $-(CR_{10}R_{20})_nY_2$;
- Y_2 is halogen, $-OR_8$, $-NO_2$, $-S(O)_mR_{11}$, $-SR_8$, $-S(O)_mNR_8R_9$, $-NR_8R_9$, $-O(CR_{10}R_{20})_nNR_8R_9$, $-C(O)R_8$, $-CO_2R_8$, $-CO_2(CR_{10}R_{20})_nCONR_8R_9$, $-ZC(O)R_8$, $-CN$, $-C(Z)NR_8R_9$, $-NR_{10}C(Z)R_8$, $-C(Z)NR_8OR_9$, $-NR_{10}C(Z)NR_8R_9$,
- 15 $-NR_{10}S(O)_mR_{11}$, $-N(OR_{21})C(Z)NR_8R_9$, $-N(OR_{21})C(Z)R_8$, $-C(=NOR_{21})R_8$, $-NR_{10}C(=NR_{15})SR_{11}$, $-NR_{10}C(=NR_{15})NR_8R_9$, $-NR_{10}C(=CR_{14}R_{24})SR_{11}$, $-NR_{10}C(=CR_{14}R_{24})NR_8R_9$, $-NR_{10}C(O)C(O)NR_8R_9$, $-NR_{10}C(O)C(O)OR_{10}$, $-C(=NR_{13})NR_8R_9$, $-C(=NOR_{13})NR_8R_9$, $-C(=NR_{13})ZR_{11}$, $-OC(Z)NR_8R_9$, $-NR_{10}S(O)_2CF_3$, $-NR_{10}C(Z)OR_{10}$, 5-(R_{18})-1,2,4-oxadiazol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl;
- 20 R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17} , excluding the moieties $-SR_5$ being $-SNR_7R_{17}$ and $-SOR_5$ being $-SOH$;
- R_6 is C_{1-4} alkyl, halo-substituted- C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{3-5} cycloalkyl;
- 25 R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22} ;
- R_8 is hydrogen, heterocyclyl, heterocyclalkyl or R_{11} ;
- 30 R_9 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R_8 and R_9 may together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12} ;
- 35 R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;
- R_{11} is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

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- R₁₂ is hydrogen, -C(Z)R₁₃ or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;
R₁₃ is hydrogen, C₁₋₁₀ alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;
- 5 R₁₄ and R₂₄ is each independently selected from hydrogen, alkyl, nitro or cyano;
R₁₅ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;
R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members
10 which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂ ;
R₁₈ and R₁₉ is each independently selected from hydrogen, C₁₋₄ alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together R₁₈ and R₁₉ denote a oxygen or sulfur;
- 15 R₂₁ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C₁₋₁₀ alkanoyl;
R₂₂ is R₁₀ or C(Z)-C₁₋₄ alkyl;
R₂₃ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;
R₃₆ is hydrogen or R₂₃;
- 20 or a pharmaceutically acceptable salt thereof.

Suitable heteroaryl moieties for R₁ and R₂ are 4-pyridyl, pyrimidinyl, quinolyl, isoquinolyl, 1-imidazolyl, 1-benzimidazolyl and thiophene, all of which may be
25 optionally substituted. Preferably, the heteroaryl group is a 4-pyridyl, 4-pyrimidinyl, 4-quinolyl, 6-isoquinolyl, 1-imidazolyl or 1-benzimidazolyl group, of which the 4-pyridyl, 4-pyrimidinyl and 4-quinolyl is more preferred. Especially preferred is the 4-pyridyl or 4-pyrimidinyl moiety, and most preferred is the 4-pyrimidinyl moiety.

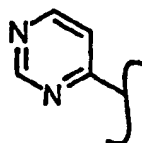
30 Suitable substituent groups for the heteroaryl moieties, R₁ and R₂, include one or two substituents each of which are independently selected from C₁₋₄ alkyl, halo, C₁₋₄ alkoxy, C₁₋₄ alkylthio, NR₁₀R₂₀ or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₂₂.

35 A preferred substituent for the heteroaryl moieties is C₁₋₄ alkyl or NR₁₀R₂₀, more preferably NR₁₀R₂₀. Preferably, when the substituent is C₁₋₄ alkyl group it is methyl. When the substituent is NR₁₀R₂₀, and R₁₀ and R₂₀ are a C₁₋₄ alkyl moiety, it is

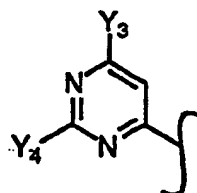
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preferably a methyl group, and more preferably R₁₀ and R₂₀ are not both C₁₋₄ alkyl groups. More preferably, both R₁₀ and R₂₀ are hydrogen or one of R₁₀ and R₂₀ are hydrogen and the other a C₁₋₄ alkyl group, especially methyl. Preferably, the 4-pyridyl group is substituted in the 2-position and the 4-pyrimidinyl group is substituted at the 2- or 4- position, more preferably the 2-position (between the two nitrogen's of the pyrimidine ring).

For the purposes herein the "core" 4-pyrimidinyl moiety is meant to be the formula:



When the 4-pyrimidinyl moiety is substituted it is preferably substituted in at least one of the following positions by the moiety Y₃ and Y₄ which are referred to herein in greater detail as optional substituents on the heteroaryl rings R₁ and R₂:



As the nomenclature will change when either Y₃ or Y₄ is substituted, for the purposes herein when Y₄ but not Y₃ is the substituted position it is referred to as the 2-position. When Y₃ but not Y₄ is the substituted position it is referred to as the 4-position and the point of attachment of the pyrimidinyl ring is the 6-position.

Suitable aryl groups for R₁ and R₂ include optionally substituted phenyl, naphth-1-yl or naphth-2-yl. The aryl ring may be optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, -C(Z)NR₇R₁₇, -C(Z)OR₂₃, -(CR₁₀R₂₀)_mCOR₃₆, -SR₅, -SOR₅, -OR₃₆, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃, or -(CR₁₀R₂₀)_mNR₁₀R₂₀ and which, for other positions of substitution, is halo, (CR₁₀R₂₀)_mcyano, -C(Z)NR₁₆R₂₆, -C(Z)OR₈, -(CR₁₀R₂₀)_mCOR₈, (CR₁₀R₂₀)_mS(O)_mR₈, (CR₁₀R₂₀)_mOR₈, halo-substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_mNR₁₀C(Z)R₈, (CR₁₀R₂₀)_mNR₁₀S(O)_mR₁₁, (CR₁₀R₂₀)_mNR₁₀S(O)_mNR₇R₁₇, (CR₁₀R₂₀)_mZC(Z)R₈ or -(CR₁₀R₂₀)_mNR₁₆R₂₆; n is 0 or an integer having a value of 1 to 10; n' is an integer having a value of 1 to 10; m is 0, or the integer 1 or 2; m' is 1 or 2; and m" is 0 or an integer having a value of 1 to 5.

Preferred substitutions for R_1 or R_2 when it is a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl moiety are one or two substituents each independently selected from halogen, -SR₅, -SOR₅, -OR₃₆, or $-(CR_{10}R_{20})_mNR_{10}R_{20}$, and for other positions of substitution on these rings preferred substitution is halogen, -S(O)_mR₈, -OR₈,
 5 $-(CR_{10}R_{20})_mNR_7R_{17}$, $(CR_{10}R_{20})_mNR_{10}C(Z)R_8$ and $-(CR_{10}R_{20})_mNR_{10}S(O)_mR_{11}$. More preferred substituents for the 4-position in phenyl and naphth-1-yl and on the 5-position in naphth-2-yl include halogen, especially fluoro and chloro, and -SR₅ and -SOR₅ wherein R₅ is preferably a C₁₋₂ alkyl, more preferably methyl; of which halogen, especially fluoro is preferred. Preferred substituents for the 3-
 10 position in phenyl and naphth-1-yl include: halogen, especially chloro; -OR₈, especially C₁₋₄ alkoxy; amino; $NR_{10}C(Z)R_8$, especially $NHCO(C_{1-10} \text{ alkyl})$; and $NR_{10}S(O)_mR_{11}$, especially $NHS(O)_2(C_{1-10} \text{ alkyl})$.

Preferably, the aryl group is an unsubstituted or substituted phenyl moiety. More preferably, it is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted
 15 at the 3-position with fluoro, chloro, C₁₋₄ alkoxy, methanesulfonamido or acetamido.

Preferably when one of R_1 or R_2 is the heteroaryl group, R_2 is the heteroaryl position.

Suitably, R_3 is $-X_c$ or $(CR_{10}R_{20})_nR_4$. When R_3 is $-X_c$ it is preferably hydrogen, $(CR_{10}R_{20})_nCH_3$, or $(CR_{10}R_{20})_nY_2$. More preferably, Y_2 includes NR_8R_9 , and
 20 $NR_{10}C(Z)R_8$ and n is 0 to 2. Most preferably, R_3 is hydrogen, methyl, amino, or acetamido.

Suitably, when R_3 is $-(CR_{10}R_{20})_nR_4$, and Q is an aryl group, then it is preferably an optionally substituted phenyl, or if Q is a heteroaryl group it is preferably a (un)
 25 substituted pyrrole, pyridine, or pyrimidine group. More preferably Q is phenyl or a substituted phenyl. All Q moieties are independently substituted by $(Y_1)_t$, wherein t is an integer of 1 to 3. Preferably t is 1 or 2. More preferably, when R_3 is monosubstituted phenyl ($t=1$), the substituent is located at the 4-position. The n term is preferably 0 to 2.

Suitably, when R_4 is $Q(Y_1)_t$ and when Y_1 is other than $(CR_{10}R_{20})_nY_2$, preferred substituents include hydrogen, halogen, or C₁₋₅ alkyl. When Y_1 is $(CR_{10}R_{20})_nY_2$ and Q
 30 is mono-substituted the substituents include $-(CR_{10}R_{20})_nY_2$ wherein: n is 0, 1, 2 or 3, preferably 0 or 1; and Y_2 is -OR₈, especially where R₈ is hydrogen or C₁₋₁₀ alkyl; -NO₂; -S(O)_mR₁₁, especially where R₁₁ is C₁₋₁₀ alkyl; -SR₈, especially where R₈ is C₁₋₁₀ alkyl; -S(O)_mNR₈R₉, especially where R₈ and R₉ is each hydrogen or C₁₋₁₀ alkyl or R₈ and R₉ together with the nitrogen to which they are attached form a 5 to 7 membered ring
 35 which optionally includes another heteroatom selected from oxygen, sulfur or NR₁₂; -NR₈R₉, especially where R₈ and R₉ is each hydrogen, methyl or benzyl or R₈ and R₉ together with the nitrogen to which they are attached form a 5 to 7 membered ring which

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optionally includes another heteroatom selected from oxygen, sulfur or NR₁₂;
 -O(CR₁₀R₂₀)_nNR₈R₉, especially where R₈ and R₉ is each C₁₋₁₀ alkyl; -C(O)R₈,
 especially where R₈ is hydrogen or C₁₋₁₀ alkyl; -CO₂R₈, especially where R₈ is hydrogen
 or C₁₋₁₀ alkyl; -CO₂(CR₁₀R₂₀)_n CONR₈R₉, especially where R₈ and R₉ is hydrogen or
 5 C₁₋₁₀ alkyl; -CN; -C(Z)NR₈R₉, especially where R₈ and R₉ is hydrogen or C₁₋₁₀ alkyl;
 -NR₁₀S(O)_mR₁₁, especially where R₁₀ is hydrogen or C₁₋₁₀ alkyl and R₁₁ is C₁₋₁₀
 alkyl or a halosubstituted; -NR₁₀C(Z)R₈, especially where R₈ is C₁₋₁₀ alkyl and R₁₀ is
 hydrogen and Z is oxygen; -C(Z)NR₈OR₉, especially where R₈ and R₉ is each hydrogen
 and Z is oxygen; -NR₁₀C(Z)NR₈R₉, especially where R₈ and R₉ is each hydrogen or
 10 C₁₋₁₀ alkyl and Z is oxygen; -N(OR₂₁)C(Z)NR₈R₉, especially where R₈ especially where
 R₈, R₉ and R₂₁ is each hydrogen or C₁₋₁₀ alkyl and Z is oxygen; -C(=NOR₁₃)NR₈R₉,
 especially where R₈, R₉ and R₁₃ is each hydrogen; -NR₁₀C(=NR₁₅)NR₈R₉, especially
 where R₈ and R₉ is hydrogen, C₁₋₁₀ alkyl or arylalkyl and R₁₅ is cyano; and 5-(R₁₈)-
 1,2,4-oxadiazol-3-yl and 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl, especially
 15 where R₁₂ is hydrogen and R₁₈ and R₁₉ is each hydrogen or C₁₋₁₀ alkyl or together are
 oxo.

More preferably, when Y₁ is (CR₁₀R₂₀)_nY₂, n is 0 to 2 and Y₂ is -OR₈, especially
 where R₈ is C₁₋₁₀ alkyl; -S(O)_mR₁₁, especially where R₁₁ is C₁₋₁₀ alkyl; -SR₈,
 especially where R₈ is C₁₋₁₀ alkyl; -NR₈R₉, especially where R₈ and R₉ is hydrogen,
 20 alkyl, aryl alkyl, or aryl or R₈ and R₉ together with the nitrogen to which they are attached
 form a pyrrolidinyl, piperidinyl or morpholinyl ring, more preferably the R₈ and R₉ terms
 in the NR₈R₉ moiety are hydrogen, methyl or benzyl; -CO₂R₈, especially where R₈ is
 hydrogen or C₁₋₁₀ alkyl; -S(O)_mNR₈R₉, especially where R₈ and R₉ is each hydrogen or
 C₁₋₁₀ alkyl; -NR₁₀S(O)_mR₁₁, especially where R₁₀ is hydrogen and R₁₁ is C₁₋₁₀ alkyl
 25 or 5-(R₁₈)-1,2,4-oxadiazol-3-yl and 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl,
 especially where R₁₂ is hydrogen and R₁₈ and R₁₉ is hydrogen or C₁₋₁₀ alkyl or together
 are oxo.

Most preferably, when Y₁ is (CR₁₀R₂₀)_nY₂, n is 0 to 2 and Y₂ is -OR₈, especially
 where R₈ is C₁₋₄; -S(O)_mR₁₁, especially where R₁₁ is C₁₋₄ alkyl; -SR₈, especially where
 30 R₈ is C₁₋₄ alkyl; -NR₈R₉, especially where R₈ and R₉ is hydrogen, C₁₋₄ alkyl, phenyl
 C₁₋₄alkyl, or phenyl or R₈ and R₉ together with the nitrogen to which they are attached
 form a pyrrolidinyl, piperidinyl or morpholinyl ring, more preferably the R₈ and R₉ terms
 in the NR₈R₉ moiety are hydrogen, methyl or benzyl. Specific embodiments of mino-
 substituted phenyls, preferably at the 4-position, are C₁₋₁₀ alkylthio, C₁₋₁₀ alkylsulfenyl,
 35 C₁₋₁₀ alkylsulfonyl, N,N-di(C₁₋₁₀ alkyl)amino C₁₋₂ alkyl, N-aralkyl-N-C₁₋₁₀ alkylamino
 C₁₋₂ alkyl, N-morpholino C₁₋₂ alkyl, C₁₋₁₀ alkylsulfonamido, sulphonamido C₁₋₂ alkyl,
 5-C₁₋₁₀ alkyl-4,5-dihydro-1,2,4-oxadiazol-3-yl or 5,5-di(C₁₋₁₀ alkyl)-4,5-dihydro-1,2,4-

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oxadiazol-3-yl. More preferably substituted with C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, or C₁₋₄ alkylsulfonyl and most preferably the C₁₋₄ alkyl is methyl.

Preferred substituents for use in R₃ when the aryl or heteroaryl group Q is disubstituted include those hereinbefore listed for use when Q is mono-substituted and, as further substituent(s), halogen and C₁₋₁₀ alkyl. When Q is phenyl substituted with two or three substituents, the alkyl moieties preferably have from one to three carbons, more preferably one. Preferred ring positions for two substituents are the 3- and 4-positions and, for three substituents, the 3-, 4- and 5- positions. The substituent at the 3- and 5-positions is preferably C₁₋₂ alkyl, such as methyl, or halogen, such as bromo, fluoro or chloro, while the substituent at the 4-position is preferably hydroxyl.

In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group, such as in R₅, R₈, R₉, or R₁₁ the unsaturated linkage, i.e., the vinylene or acetylene linkage is preferably not directly attached to the nitrogen, oxygen or sulfur moieties, for instance in Y₂ as C(Z)NR₈OR₉, NR₁₀C(Z)NR₈R₉, or OR₈.

As used herein, "optionally substituted" unless specified, refers to such groups as halogen, hydroxyl, alkoxy, S(O)_m C₁₋₆ alkyl, amino, a mono & di-substituted amino, such as an NR₇R₁₇ group, C₁₋₆ alkyl, halo substituted C₁₋₆ alkyl, C₃₋₇ cycloalkyl, an optionally substituted aryl or an optionally substituted arylalkyl wherein the substituents are halogen, hydroxyl, alkoxy, S(O)_m C₁₋₆ alkyl, amino, a mono & di-substituted amino, such as an NR₇R₁₇ group, C₁₋₆ alkyl, or halo substituted C₁₋₆ alkyl, unless otherwise specified herein.

When R₃ includes a X_a-P(Z)(X_bR₁₃)₂ group linked either directly to the oxazole ring or indirectly *via* an aryl or heteroaryl group, X_a is suitably oxygen or C₁₋₄ alkylene, optionally interrupted by oxygen, for instance -CH₂OCH₂- and Z and X_b is each oxygen, such that the preferred groups include -OP(O)(OR₁₃)₂ and -CH₂OCH₂-P(O)(OR₁₃)₂.

In a preferred subgenus of compounds of formula (I), one of R₁ or R₂ is 4-pyridyl, 2-alkyl-4-pyridyl, 2-NR₁₀R₂₀-4-pyridyl, 4-pyrimidinyl, 2-alkyl-pyrimidin-4-yl, 2-NR₁₀R₂₀-pyrimidin-4-yl, 4-NR₁₀R₂₀-pyrimidin-6-yl, or 4-quinolyl. Preferably R₃ is hydrogen, methyl, amino, or acetamido or phenyl or phenyl substituted with a substituent selected from -(CR₁₀R₂₀)_nY₂ wherein n is 0, 1, 2 or 3 and Y₂ is -OR₈, -NO₂, -S(O)_mR₁₁, -SR₈, -S(O)_mNR₈R₉, -NR₈R₉, -O(CR₁₀R₂₀)_nNR₈R₉, -C(O)R₈, -CO₂R₈, -CO₂(CR₁₀R₂₀)_nCONR₈R₉, -CN, -C(Z)NR₈R₉, -C(Z)NR₈OR₉, -NR₁₀S(O)_mR₁₁, -NR₁₀C(Z)R₈, -NR₁₀C(Z)NR₈R₉, -C(=NOR₁₃)NR₈R₉, -NR₁₀C(=CR₁₄R₂₄)NR₈R₉, 5-(R₁₈)-1,2,4-oxadiazol-3-yl, 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl, a 3,5-dimethyl or dibromo-4-hydroxyl grouping, wherein the substituent is preferably at the 4-position; and the other of one of R₁ or R₂ is phenyl or phenyl substituted by fluoro, chloro, C₁₋₄ alkoxy, S(O)_m C₁₋₄ alkyl, methanesulfonamido or acetamido. Preferably R₁ is the

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optionally substituted phenyl. More preferably R₃ is hydrogen, methyl, amino, or acetamido or phenyl substituted at the 4-position with C₁₋₁₀ alkylthio, C₁₋₁₀ alkylsulfinyl, C₁₋₁₀ alkylsulfonyl.

5 In a more preferred subgenus R₃ is hydrogen, methyl, amino, or acetamido or phenyl substituted at the 4-position with C₁₋₁₀ alkylthio, C₁₋₁₀ alkylsulfinyl, C₁₋₁₀ alkylsulfonyl; and one of R₁ or R₂ is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro, C₁₋₄ alkoxy, methane-sulfonamido or acetamido; and the other of R₁ or R₂ is 4-pyridyl, 2-alkyl-4-pyridyl, 2-NR₁₀R₂₀-4-pyridyl, 4-pyrimidinyl, 2-alkyl-pyrimidin-4-yl, 2-NR₁₀R₂₀-pyrimidin-4-yl, 10 4-NR₁₀R₂₀-pyrimidin-6-yl, or 4-quinolyl. More preferably one of R₁ or R₂ is an NR₁₀R₂₀ substituted pyrimidinyl and most preferably it is the R₂ moiety.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, 15 hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent 20 Y₁ in R₃ comprises a carboxy group. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

- 25
- "halo" - all halogens, that is chloro, fluoro, bromo and iodo;
 - "C₁₋₁₀alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like;
 - The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 7 30 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like;
 - The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like;
- 35
- "aryl" - phenyl and naphthyl;
 - "heteroaryl" (on its own or in any combination, such as "heteroaryloxy") - a 5-10 membered aromatic ring system in which one or more rings contain one or more

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heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, thiophene, quinoline, isoquinoline, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole;

5 • "heterocyclic" (on its own or in any combination, such as "heterocyclalkyl") - a saturated or wholly or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine or pyrazolidine;

10 • The term "alkyl" or "heteroarylalkyl" or "heterocyclalkyl" is used herein to mean C₁₋₄ alkyl as defined above unless otherwise indicated;

 • "aroyl" - a C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivatives, such as benzyl and the like;

 • "alkanoyl" - a C(O)C₁₋₁₀alkyl wherein the alkyl is as defined above;

15 • "sulfinyl" - the oxide S(O) of the corresponding sulfide while the term "thio" refers to the sulfide.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

20

Exemplified compounds of formula (I) include:

5-(3-Methoxyphenyl)-2-methyl-4-(4-pyridyl)oxazole;

5-(4-Fluorophenyl)-2-methyl-4-(4-pyridyl)oxazole;

4-(4-Fluorophenyl)-5-(4-pyridyl)oxazole;

25 4-(3-Chlorophenyl)-5-(4-pyridyl)oxazole;

2-Amino-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole;

2-Dimethylamino-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole;

4-(4-Fluorophenyl)-5-(4-pyrimidinyl)oxazole;

4-(4-Fluorophenyl)-5-(2-aminopyrimidin-4-yl)oxazole;

30 4-(4-Fluorophenyl)-5-(2-methylaminopyrimidin-4-yl)oxazole;

4-(4-Fluorophenyl)-5-(2-dimethylaminopyrimidin-4-yl)oxazole;

4-(4-Fluorophenyl)-5-(2-methylthiopyrimidin-4-yl)oxazole;

4-(3-Chlorophenyl)-5-(2-methylpyrid-4-yl)oxazole;

4-(4-Fluorophenyl)-2-methyl-5-(4-pyridyl)oxazole;

35 4-(4-Fluorophenyl)-2-methyl-5-(4-quinolyl)oxazole;

5-(4-Fluorophenyl)-4-(2-aminopyrimidin-4-yl)oxazole;

2-Amino-5-(4-fluorophenyl)-4-(4-pyridyl)oxazole; and

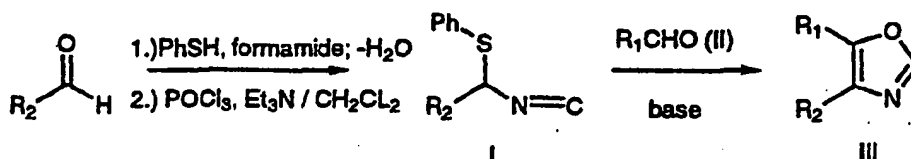
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2-Dimethylamino-5-(4-fluorophenyl)-4-(4-pyridyl)oxazole.

Preferred compounds of formula (I) include:

- 5-(3-Methoxyphenyl)-2-methyl-4-(4-pyridyl)oxazole;
- 5 5-(4-Fluorophenyl)-2-methyl-4-(4-pyridyl)oxazole;
- 2-Methyl-4-(Phenyl)-5-(4-pyridyl)oxazole;
- 4-(4-Fluorophenyl)-2-methyl-5-(4-pyridyl)oxazole;
- 4-(4-Fluorophenyl)-2-phenyl-5-(4-pyridyl)oxazole;
- 2-Amino-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole.
- 10 4-(4-Fluorophenyl)-5-(4-pyridyl)oxazole;
- 4-(4-Fluorophenyl)-5-(2-methylpyrid-4-yl)oxazole;
- 4-(3,4-Dichlorophenyl)-5-(4-pyridyl)oxazole;
- 4-(3-Chlorophenyl)-5-(4-pyridyl)oxazole;
- 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)oxazole;
- 15 4-(4-Fluorophenyl)-2-[4-(methylsulfinyl)phenyl]-5-(4-pyridyl)oxazole;
- 4-(4-Fluorophenyl)-5-(2-aminopyrimidin-4-yl)oxazole; and
- 2-Acetamido-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole.

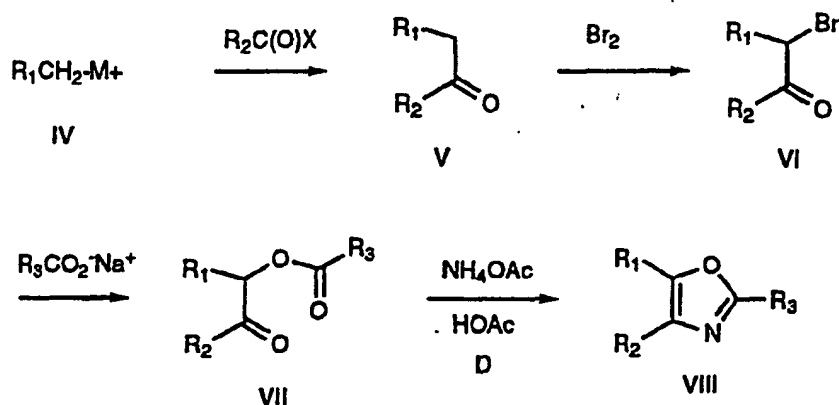
20 Compounds of Formula (I) are oxazole derivatives which may be readily prepared using procedures well known to those of skill in the art and may be prepared by analogous methods to those indicated herein below.



Scheme I

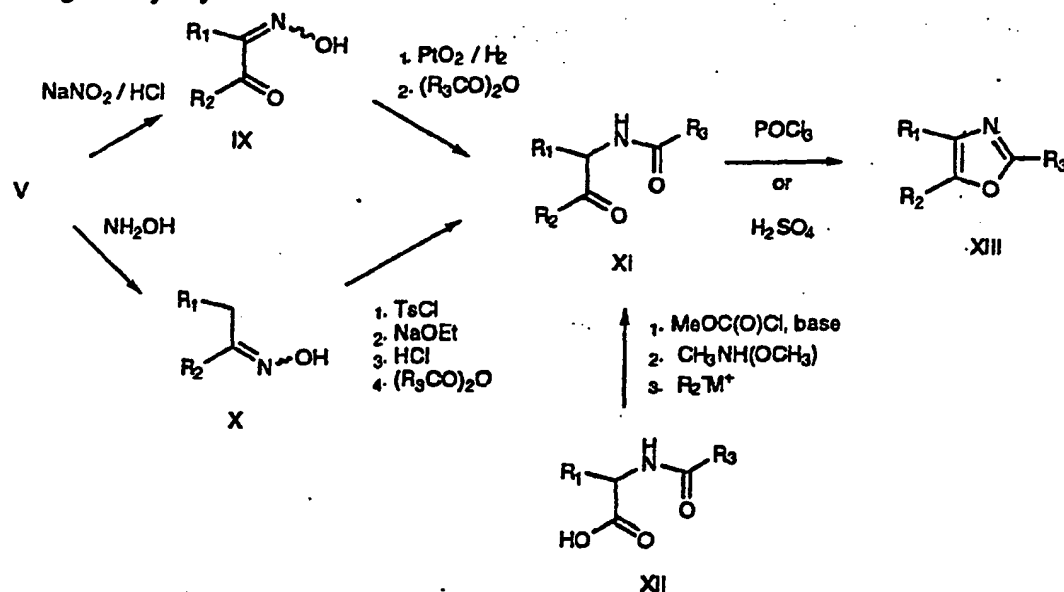
25 Scheme I illustrates the preparation of oxazoles which are substituted only by a hydrogen at C-2 ($R_3 = H$). The requisite aldehydes wherein R_2 and R_1 are defined as in formula (I) or suitably protected precursors thereof can be prepared from readily available materials using standard transformations known to one skilled in the art. The isonitrile (I) is prepared from an aldehyde (R_2COH), formamide and a thiol or a sulfinic acid (preferably as aryl compounds) in a 3 component condensation. For a more detailed description see Example 7 herein. Reaction of I with aldehyde II is initiated with a suitable base, for
 30 example a guanidine base such as 1,5,7 triazobicyclo[4.4.0]dec-5-ene, in an inert solvent such as methylene chloride or DME yields oxazole III.

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Scheme II

Scheme II illustrates the preparation of oxazoles possessing an alkyl group at C-2 (VIII) by cyclization of an appropriate acyloxyketone VII with NH_4OAc / $HOAc$. Compound VII can be prepared as illustrated in three steps from the desired organometallic derivative IV. A relevant example of the first step, preparation of ketone V, is outlined in Scheme II of PCT/US93/00674, Adams et al., published as WO93/14081 whose disclosure is incorporated by reference herein in its entirety. Compound V can be brominated to afford bromoketone VI. Displacement of the bromide by the sodium salt of a carboxylic acid gives acyloxyketone VII.

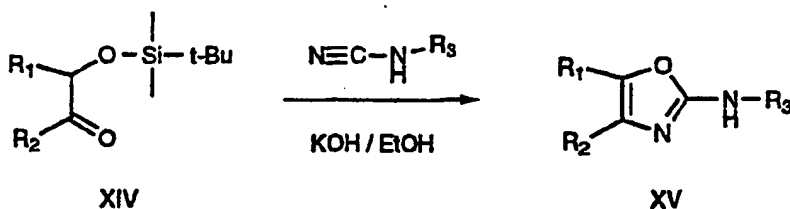


Scheme III

Scheme III illustrates an alternative route to the preparation of oxazoles possessing an alkyl substituent at C-2 (XIII). The procedure involves cyclizing the appropriate

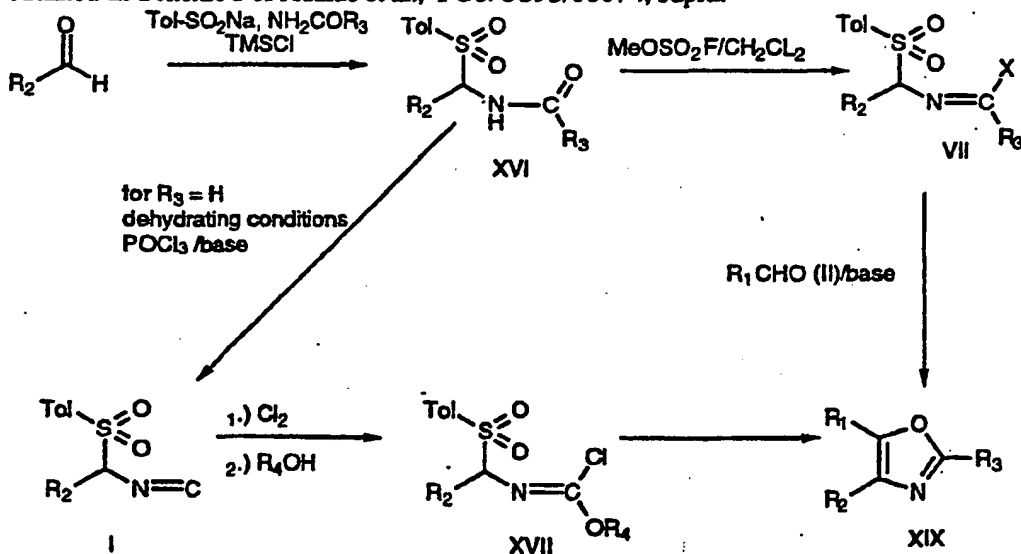
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- acylaminoketone XI under dehydrating conditions. Three methods of preparing compound XI are shown. Two of the methods start with ketone V. In one method, compound V can be converted to the oximinoketone IX using either acidic conditions with an aqueous solution of an alkali nitrite salt or employing basic conditions in alcoholic solvents with an alkyl nitrite, for example, potassium t-butoxide in t-butanol plus amyl nitrite. Subsequent reduction of the oximinoketone IX, preferably with hydrogen and a metal catalyst yields an aminoketone which may be prepared and isolated under acidic conditions to afford initially the hydrohalide salt which is in a separate step acylated to produce compound XI or acylated in situ to yield directly compound XI. In the other method, the corresponding oxime (X) of V can be converted, via a Neber reaction, to an aminoketone which after acylation affords XI. The third method produces XI by the addition of an organometallic derivative of R₂ to the acylated and activated derivative of the α-amino acid of R₁.



Scheme IV

- Scheme IV illustrates the preparation of 2-aminooxazoles XV. They can be prepared from silyloxyketone XIV and the desired cyanamide using the procedure described by Cockerill, A. F., et al., *Syn.*, 1976, 591. The preparation of compound XIV is outlined in Scheme I of Adams et al., PCT/US93/00674, *supra*.



Scheme V

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The route illustrated in Scheme V allows for the preparation of 2-substituted oxzaoles in which the R₃ group can be either the direct attachment of a carbon (alkyl or aryl) or an oxygen or sulfur heteroatom linker. The synthesis of the tosyl amides (XVI) and subsequent dehydration to the isonitrile (I) is analogous to that outlined in Scheme I, but yields products with the sulfur leaving group at the sulfone instead of sulfide oxidation state. Either oxidation state of sulfur is applicable to the processes outlined in Schemes I and V. Alkylation of the amide XVI on oxygen or sulfur (if a thioamide is used) using an oxonium salt or under other conditions known to favor heteroatom versus carbon alkylation yields the imine XVII. Reaction of XVII with aldehyde II under the basic conditions required to initiate cycloaddition produces the oxazole XIX. Alternatively, the isonitrile I may be used to prepare chloroimidates (XVIII) which also undergo the base-induced cyclization with aldehyde II. Experimental procedures for the cyclization to the oxazole and the preparation of the intermediates are outlined in the following articles: A.M. van Leuson et. al. in *Tet. Let.*, p143 (1976); *J. Heterocyclic Chem.*, 18, p1127 & p1133 (1981) whose disclosure is incorporated by reference herein in its entirety.

Once the oxazole nucleus has been established, further compounds of formula (I) may be prepared by applying standard techniques for functional group interconversion, for instance: -C(O)NR₈R₉ from -CO₂CH₃ by heating with or without catalytic metal cyanide, e.g. NaCN, and HNR₈R₉ in CH₃OH; -OC(O)R₈ from -OH with e.g., ClC(O)R₈ in pyridine; -NR₁₀-C(S)NR₈R₉ from -NHR₁₀ with an alkylisothiocyanate or thiocyanic acid; NR₆C(O)OR₆ from -NHR₆ with the alkyl chloroformate; -NR₁₀C(O)NR₈R₉ from -NHR₁₀ by treatment with an isocyanate, e.g. HN=C=O or R₁₀N=C=O; -NR₁₀-C(O)R₈ from -NHR₁₀ by treatment with Cl-C(O)R₈ in pyridine; -C(=NR₁₀)NR₈R₉ from -C(NR₈R₉)SR₈ with H₃NR₈⁺OAc⁻ by heating in alcohol; -C(NR₈R₉)SR₈ from -C(S)NR₈R₉ with R₆-I in an inert solvent, e.g. acetone; -C(S)NR₈R₉ (where R₈ or R₉ is not hydrogen) from -C(S)NH₂ with HNR₈R₉; -C(=NCN)-NR₈R₉ from -C(=NR₈R₉)-SR₈ with NH₂CN by heating in anhydrous alcohol, alternatively from -C(=NH)-NR₈R₉ by treatment with BrCN and NaOEt in EtOH; -NR₁₀-C(=NCN)SR₈ from -NHR₁₀ by treatment with (R₈S)₂C=NCN; -NR₁₀SO₂R₈ from -NHR₁₀ by treatment with ClSO₂R₈ by heating in pyridine; -NR₁₀C(S)R₈ from -NR₁₀C(O)R₈ by treatment with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; -NR₁₀SO₂CF₃ from -NHR₆ with triflic anhydride and base; -NR₁₀C(O)-C(O)-OR₈ from -NHR₁₀ with, e.g. methyloxalyl chloride and a base such as triethylamine; -NR₁₀C(O)-C(O)-NR₈R₉ from -NR₁₀C(O)-C(O)-OR₈ with HNR₈R₉; and 1-(NR₁₀)-2-imidazolyl from -C(=NH)NHR₁₀ by heating with 2-chloroacetaldehyde in chloroform (wherein R₆, R₈, R₉ and R₁₀ are as hereinbefore defined).

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Suitable protecting groups for use with hydroxyl groups, for instance, are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981 whose disclosure is incorporated by reference herein. Suitable examples of hydroxyl protecting groups include silyl ethers, such as t-butyldimethyl or t-butyl-diphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, (CR_{10R20})_n.

Pharmaceutically acid addition salts of compounds of formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

Synthetic Examples

Example 1

5-(3-Methoxyphenyl)-2-methyl-4-(4-pyridyl)oxazole

(a) 2-Amino-1-(3-methoxyphenyl)-2-(4-pyridyl)acetophenone hydrochloride - The title compound was prepared following the procedure of Murphy, J.G. *J. Org. Chem.*, 1961, 26, 3104 except using 2-hydroxyimino-1-(3-methoxyphenyl)-2-(4-pyridyl)acetophenone [see PCT/US93/00674, Adams et al., published as WO93/14081].

(b) 2-Acetamido-1-(3-methoxyphenyl)-2-(4-pyridyl)ethanone - To a solution of 2-amino-3-methoxy-2-(4-pyridyl)acetophenone hydrochloride (0.5 g, 1.8 mmol) in pyridine (8 mL) was added acetic anhydride (1 mL). The mixture was stirred at rt for 45 min, then poured into H₂O. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with sat'd NaCl, then dried over MgSO₄. Evaporation of solvent gave a red oil which was purified by flash chromatography, eluting with a solvent gradient of 0-4% MeOH/CHCl₃. The title compound was isolated as a yellow oil (0.21 g).

(c) 5-(3-Methoxyphenyl)-2-methyl-4-(4-pyridyl)oxazole - The title compound was prepared using the procedure of Hayes, F.N. *et al.*, *J. Amer. Chem Soc.*, 1955, 77, 1850 except using 2-acetamido-1-(3-methoxyphenyl)-2-(4-pyridyl)ethanone: ESMS (*m/z*): 267 (M⁺+H).

Example 2

5-(4-Fluorophenyl)-2-methyl-4-(4-pyridyl)oxazole

(a) 1-(4-Fluorophenyl)-2-(4-pyridyl)ethanone oxime - To a solution of 4-fluorophenyl-2-(4-pyridyl)acetophenone (8.08 g, 37.6 mmol) [See PCT/US93/00674, Adams et al.,

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WO93/14081] in EtOH (80 mL) was added hydroxylamine hydrochloride (4.12 g, 59.7 mmol) and pyridine (4.8 mL, 59.7 mmol). The mixture was stirred at 60 °C for 1 h, then poured into H₂O and stirred an additional 1 min. The resulting precipitate was filtered and washed with H₂O. The precipitate was recrystallized from EtOH/H₂O to give the title compound as a white solid (6.29 g): mp 135-136 °C.

(b) 2-Acetamido-1-(4-fluorophenyl)-2-(4-pyridyl)ethanone - The title compound was prepared by the procedure of Shilcrat, S.C. *et al.*, *J. Heterocyclic Chem.*, 1991, 28, 1181 except using 1-(4-fluorophenyl)-2-(4-pyridyl)ethanone oxime and acetic anhydride.

(c) 5-(4-Fluorophenyl)-2-methyl-4-(4-pyridyl)oxazole - The title compound was prepared using the procedure of Hayes, F.N. *et al.*, *J. Amer. Chem. Soc.*, 1955, 77, 1850 except using 2-acetamido-1-(4-fluorophenyl)-2-(4-pyridyl)ethanone: ESMS (*m/z*): 255 (M⁺+H).

Example 3

2-Methyl-4-phenyl-5-(4-pyridyl)oxazole

(a) 2-Phenyl-1-(4-pyridyl)acetophenone - A suspension of isonicotinoyl chloride (0.58 g, 3.26 mmol) in dry THF (7.0 mL) was cooled to -78 °C, and benzyl magnesium chloride (3.4 mL, 6.85 mmol; 2.0 M soln in THF) was added dropwise. After the addition was complete, the ice bath was removed and the reaction mixture was allowed to warm to room temperature. After 3 h the reaction mixture was poured into saturated NH₄Cl and the layers were separated. The aqueous mixture was extracted with THF. The combined organic layers were washed with sat'd NaCl and dried over MgSO₄. Evaporation of solvent gave a yellow solid which was purified by flash chromatography, eluting with a solvent gradient of 0-3% MeOH/CH₂Cl₂. The title compound was isolated as a yellow solid (0.50 g).

(b) 1-Hydroxyimino-1-phenyl-1-(4-pyridyl) ethanone - To a solution of 2-phenyl-1-(4-pyridyl)acetophenone (0.50 g, 2.53 mmol) in pyridine (7.5 mL) was added hydroxylamine hydrochloride (0.65 g, 9.36 mmol). After stirring at rt for 20 h, the pyridine was evaporated and the residue was taken up in H₂O and filtered. The precipitate was washed with H₂O and air-dried giving the title compound as a yellow solid (0.529 g).

(c) 2-Acetamido-2-(4-phenyl)-1-(4-pyridyl)ethanone - Sodium (0.08 g, 3.50 mmol) was added to absolute EtOH (16 mL) and stirred. Upon completion of the reaction and cooling to ambient temperature, 1-Hydroxyimino-2-phenyl-1-(4-pyridyl)ethanone (0.53 g, 2.50 mmol) was added portionwise. After 15 min, the yellow reaction mixture was cooled in an ice-bath and *p*-toluenesulfonyl chloride (0.59 g, 3.07 mmol) was added in a single portion. The mixture was stirred at -5 °C for 2 h and then a solution of NaOEt [from sodium (0.07 g, 5.18 mmol) and absolute EtOH (3.3 mL)] was added dropwise. After 45 min, Et₂O (9 mL) was added and the stirring was continued. After 30 min, the solvent was evaporated and the residue was partitioned between Et₂O and 3N HCl. The layers were separated and

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- the Et₂O layer was extracted with HCl. The aqueous phase was evaporated to give a yellow oil (1.52 g) which was dissolved in pyridine (10 mL). Acetic anhydride (1 mL) was added and the reaction mixture was stirred at rt. After 19 h, the mixture was poured into H₂O and CH₂Cl₂ was added. The layers were separated and the aqueous layer was
- 5 extracted with CH₂Cl₂. The combined organic layers were washed with sat'd NaCl and dried over MgSO₄. Evaporation of solvent gave a red oil which was purified by flash chromatography, eluting with 0-3% MeOH/CHCl₃. The title compound was obtained as a gold oil (0.238 g).
- (d) 2-Methyl-4-phenyl-5-(4-pyridyl)oxazole - A mixture of 2-acetamido-2-phenyl-1-(4-pyridyl)ethanone (0.101 g, 0.397 mmol) in conc. H₂SO₄ (1 mL) was heated at 100 °C for
- 10 18 h. After cooling, the mixture was poured onto ice and neutralized with 2.5N NaOH. The aqueous mixture was extracted with CH₂Cl₂ and the combined organic extracts were washed with sat'd NaCl and dried over MgSO₄. Evaporation of solvent gave an oil which was purified by flash chromatography, eluting with 0-2% MeOH/CHCl₃. The title
- 15 compound was obtained as a gold oil (3.0 mg): MS(DCI/NH₃) (*m/z*): 237 (M⁺+H).

Example 4

4-(4-Fluorophenyl)-2-methyl-5-(4-pyridyl)oxazole

- To a solution of 4-fluorophenyl-2-(4-pyridyl)acetophenone [See PCT/US93/00674, Adams et al., published as WO93/14081] (0.167 g, 0.76 mmol) in CH₂Cl₂ (5 mL) was added
- 20 bromine (7.8 mL, 0.78 mmol; 0.1M soln in CH₂Cl₂). After stirring at room temperature for 30 min, the solvent was removed *in vacuo* and the solid was taken up in glacial acetic acid (10 mL). Sodium acetate (0.192 g, 2.34 mmol) and ammonium acetate (0.301 g, 3.9 mmol) were added and the reaction mixture was heated at reflux for 19 h. After cooling, the
- 25 mixture was poured into H₂O, neutralized with conc. NH₄OH, then extracted exhaustively with CH₂Cl₂. The combined organic layers were washed with sat'd NaCl and dried over MgSO₄. Evaporation of solvent provided a yellow solid which was purified by flash chromatography, eluting with 100% CHCl₃. The title compound was obtained as a yellow waxy solid (0.067 g): ESMS (*m/z*): 255 (M⁺+H).

30

Example 5

4-(4-Fluorophenyl)-2-phenyl-5-(4-pyridyl)oxazole

- (a) 2-Benzoyloxy-1-(4-fluorophenyl)-2-(4-pyridyl)ethanone - To a solution of 4-fluorophenyl-2-(4-pyridyl)acetophenone [See PCT/US93/00674, Adams et al., published as WO93/14081 (0.356 g, 1.65 mmol) in CH₂Cl₂ (5 mL) was added bromine (18.1 mL,
- 35 1.81 mmol; 0.1M soln in CH₂Cl₂). After stirring at rt for 30 min, the solvent was removed *in vacuo* and the solid was taken up in EtOH (5 mL). Sodium benzoate (0.635 g, 4.4 mmol)

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and conc. H₂SO₄ (3 drops) were added and the mixture was heated at reflux for 18 h. After cooling, the mixture was poured into H₂O, neutralized with conc. NH₄OH, then extracted with EtOAc. The combined organic extracts were washed with sat'd NaCl and dried over MgSO₄. Evaporation of solvent gave a red oil which was filtered through a pad of silica gel, eluting with a solvent gradient of 100:0 to 50:1 CHCl₃/MeOH. The title compound

- 5 was isolated as a yellow oil (0.131 g).
(b) 4-(4-Fluorophenyl)-2-phenyl-5-(4-pyridyl)oxazole - A solution of 2-benzoyloxy-1-(4-fluorophenyl)-2-(4-pyridyl)ethanone (0.131 g, 0.391 mmol) and ammonium acetate (0.28 g, 3.63 mmol) in glacial acetic acid (3 mL) was heated at reflux for 1.5 h. After
10 cooling, the mixture was neutralized with conc. NH₄OH and the solvent was removed *in vacuo* to give a yellow oil. Purification by flash chromatography (15-25% EtOAc/Hex) afforded the title compound as a white solid (9.0 mg): ESMS (*m/z*): 317 (M⁺+H).

Example 6

- 15 2-Amino-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole
A mixture of 1-(*t*-butyldimethylsilyloxy)-2-(4-fluorophenyl)-1-(4-pyridyl)ethanone [See Ex. 79 (a) of Adams et al., WO93/14081] (5.16 g, 15.0 mmol), cyanamide (0.95 g, 22.5 mmol) and KOH (0.55 g, 9.8 mmol) in EtOH (20 mL) was heated at reflux for 1 h. After cooling, the precipitate was filtered and washed with EtOH. Recrystallization from
20 CH₂Cl₂/MeOH afforded the title compound as a yellow solid (0.38 g): ESMS (*m/z*): 256 (M⁺+H).

Example 7

- 4-(4-Fluorophenyl)-5-(4-pyridyl)oxazole
25 a) 4'-fluorophenyl-(tolylthio)methylformamide
A soln of p-Fluorobenzaldehyde (13.1 mL, 122 mmol) thiocresol (16.64 g, 122 mmol), formamide (15.0 mL, 445 mmol), and toluene (300 mL) were combined and heated to toluene reflux with azeotropic removal of H₂O for 18 h. The cooled reaction was diluted with EtOAc (500 mL) and washed with satd aq Na₂CO₃ (3 x 100 mL), satd aq NaCl (100
30 mL), dried (Na₂SO₄), and concentrated. The residue was triturated with petroleum ether, filtered and dried *in vacuo* to afford 28.50 g of the title compound as a white solid (85 %). mp = 119 - 120°.
b) 4'-fluorophenyl-(tolylthio)methylisocyanide
4-Fluorophenyl-(tolylthio)methylformamide (25 g, 91 mmol) in CH₂Cl₂ (300 mL)
35 was cooled to -30 ° and, with mechanical stirring, POCl₃ (11 mL, 110 mmol) was added dropwise followed by the dropwise addition of Et₃N (45 mL, 320 mmol) with the temperature maintained below -30 °. Stirred at -30 ° for 30 min and 5 ° for 2 h, diluted

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with CH_2Cl_2 (300 mL) and washed with 5% aq Na_2CO_3 (3 x 100 mL), dried (Na_2SO_4) and concentrated to 500 mL. This soln was filtered through a 12 x 16 cm cylinder of silica in a large sintered glass funnel with CH_2Cl_2 to afford 12.5 g (53%) of purified isonitrile as a light brown, waxy solid. IR (CH_2Cl_2) 2130 cm^{-1} .

5 c) 4-(4-Fluorophenyl)-5-(4-pyridyl)oxazole

4-Fluorophenyl-(tolylthio)methylisocyanide (2.57 g, 10 mmol), pyridine-4-carboxaldehyde (1.07 g, 10 mmol) and CH_2Cl_2 (20 mL) were stirred under Ar at -15° (ice-methanol bath) and TBD (1.39 g, 10 mmol) was added portionwise. The reaction temperature rose to 5° before recooling to -15° . The reaction was allowed to warm to 4° and was kept at that temperature for 18 h, diluted with EtOAc (100 mL) and washed with 10% aq Na_2CO_3 (3 x 25 mL). The EtOAc was then extracted with 1 N HCl (3 x 15 mL) and crystals formed from the aqueous phase. After standing for 1 h at 23° the crystals were filtered off, washed with abs EtOH (25 mL) and Et_2O (2 x 25 mL) and dried in vacuo to afford 1.47 g (53%) of the title cmpd as the hydrochloride. The aq filtrate was washed with EtOAc (2 x 40 mL) and made basic by the careful addition of solid K_2CO_3 . Extraction of with EtOAc (3 x 40 mL) drying (Na_2SO_4) concentration and crystallization of the residue (hexane/acetone) afforded an additional 0.426 g (18%) of the title compound as the free base, mp (free base) = $110-111^\circ$.

20

Example 8

4-(4-Fluorophenyl)-5-(2-methylpyrid-4-yl)oxazole

The compound of example 7(b) (0.599 g, 2.33 mmol) and 2-methylpyridine 4-carboxaldehyde (257 mg, 2.12 mmol) and CH_2Cl_2 (4 mL) were reacted by the procedure of Example 7. The resulting reaction was worked up by dilution with EtOAc (40 mL), washing with satd aq Na_2CO_3 (2 x 15 mL), extraction of the EtOAc with 1N HCl (3 x 15 mL). The combined aq phases were washed with EtOAc (3 x 25 mL) and then made basic by the careful addition of K_2CO_3 . Extraction of the aq with EtOAc (4 x 40 mL), drying (Na_2SO_4) and concentration afforded a tan oil which could not be made to solidify. The residue was dissolved in 9:1 Et_2O /acetone (20 mL) and 1N ethereal HCl (3 mL) was added. The precipitated solid was washed with Et_2O and dried in vacuo to afford 471 mg (79%) of the title compound as the hydrochloride, mp = $198-200$ (dec).

30

Example 9

4-(3,4-Dichlorophenyl)-5-(4-pyridyl)oxazole

35 Using the method of example 7 (a,b,c) substituting 3,4,-dichlorobenzaldehyde for 4-fluorobenzaldehyde the title compound was prepared. mp = 142° .

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Example 10**4-(3-Chlorophenyl)-5-(4-pyridyl)oxazole**

Using the method of example 7 (a,b,c) substituting 3-chlorobenzaldehyde for 4-fluorobenzaldehyde the title compound was prepared. mp = 125-126°.

5

Example 11**4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)oxazole**

(a) 2-(4-Fluorophenyl)-1-(4-pyridyl)-2-oxoethyl 4-methylthiobenzoate and 1-(4-Fluorophenyl)-2-(4-pyridyl)-2-oxoethyl 4-methylthiobenzoate - The title compounds were prepared using the same procedure of Lantos *et al.* (*J. Med. Chem.* 1984, 27, 72) whose disclosure is incorporated by reference herein, and used to prepare 1-(4-fluorophenyl)-2-(4-pyridyl)-2-oxoethyl benzoate and 2-(4-fluorophenyl)-1-(4-pyridyl)-2-oxoethyl benzoate, except using 1-cyano-1-(4-pyridyl)methyl 4-methylthiobenzoate.

10

(b) 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)oxazole - To a solution containing a mixture of 2-(4-fluorophenyl)-1-(4-pyridyl)-2-oxoethyl 4-methylthiobenzoate and 1-(4-fluorophenyl)-2-(4-pyridyl)-2-oxoethyl 4-methylthiobenzoate (1.0 g, 2.62 mmol) in glacial acetic acid (50 mL) was added ammonium acetate (2.0 g, 26.2 mmol). The resulting mixture was heated at reflux for 1.5 h, then allowed to cool. The mixture was poured into H₂O, neutralized with conc. NH₄OH and extracted with CH₂Cl₂. The combined organic extracts were washed with sat'd NaCl and dried over MgSO₄. Purification by column chromatography, eluting with 5:1 to 1:1 Hex/EtOAc afforded the title compound (77.6 mg) as a yellow solid: ESMS (*m/z*): 363.0 (M⁺+H).

15

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Example 12**4-(4-Fluorophenyl)-2-[4-(methylsulfinyl)phenyl]-5-(4-pyridyl)oxazole**

To a mixture of 4-(4-fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)oxazole (0.056 g, 0.15 mmol) in glacial acetic acid (12 mL) was added a solution of K₂S₂O₈ (0.07 g, 0.24 mmol) in H₂O (2 mL). After stirring at rt for 48 hr, the precipitate was filtered. Purification by column chromatography (25:1 CH₂Cl₂/MeOH), followed by trituration with Et₂O afforded the title compound (0.014 g) as a white solid: ESMS (*m/z*) = 379.0 (M⁺+H).

25

30

Example 13**2-Acetamido-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole**

A mixture of 2-amino-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole (0.090 g, 0.353 mmol) in acetic anhydride (4 mL) was stirred at room temperature. After 72 h the mixture was poured into H₂O and neutralized with conc. NH₄OH. The resulting precipitate was filtered and washed with H₂O. Purification by column chromatography (0-5% MeOH/CHCl₃).

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followed by recrystallization from MeOH afforded the title compound as a white solid (30.0 mg): ESMS (m/z): 298.0 ($M^+ + H$).

Example 14

5 4-(4-Fluorophenyl)-5-(2-amino-4-pyrimidinyl)oxazole

a) 1-N,N-dimethylamino-(4,4-dimethoxy)buten-3-one

Pyruvic aldehyde dimethyl acetal (50 ml, 0.4106 mol) and N,N-Dimethylformamide dimethyl acetal (54.5 ml, 0.4106 mol) were mixed neat and heated to 80 °C for eighteen hours. Crude product (95.0 g) was used without further purification.

10 b) 2-Amino-4-(dimethoxymethyl)pyrimidine

Guanidine HCl (43 g) was mixed in water (150 ml) and added to 1-N,N-dimethylamino-(4,4-dimethoxy)buten-3-one (95.0 g, crude) at room temperature. Sodium hydroxide was mixed in water and added to reaction mixture at room temperature. The reaction was then heated to 60 °C for eighteen hours. A precipitate formed and was
15 filtered and washed with water. The crude product (32.5 g) was used without further purification.

c) 2-Amino-(pyrimidinyl)aldehyde

2-Amino-4-(dimethoxymethyl)pyrimidine (6.6g, 0.0390 mol) was mixed in 3N HCl (29.96 ml, 0.0858) neat and heated to 47 °C for sixteen hours. The reaction was cooled to
20 room temperature and ethyl acetate (150 ml) was added. NaHCO₃ (16.17 g, 0.1716 mol) was then added slowly. The mixture was stirred and the organic layer decanted, this was repeated a total of five times. The organic phases were combined and evaporated to yield the product - a yellow solid (2.33g, 48 %). ¹H NMR (400 MHz, CDCl₃) δ 9.80 (s, 1H), 8.50 (d, 1H), 7.08 (d, 1H) 5.25 (s broad, 2H).

25 d) 2-Aminopyrimidine-[2,2,6,6-tetramethylpiperidinyl]imine

2-Amino-(pyrimidin-4-yl)aldehyde (2.33 g, 0.0189 mol) and 4-Amino-(2,2,6,6-tetramethyl)piperidine (3.24 ml, 0.0189) were mixed in CH₂Cl₂ at room temperature for eight hours to yield the crude product (which contains the imine plus a large, approx. equal amount of unreacted 2-amino-(pyrimidin-4-yl)aldehyde) (4.92 g) which was used without
30 further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, 1H), 8.20 (s, 1H), 7.25 (d, 1H), 5.10 (s broad, 2H), 1.79 (m, 1H) 1.70 (m, 1H), 1.40 (t, 2H), 1.30-1.00 (m, 12H), 0.85 (t, 2H).

e) 4-(4-Fluorophenyl)-5-(2-amino-4-pyrimidinyl)oxazole

The crude mixture from step (d) above (4.92 g) was mixed in CH₂Cl₂ and cooled to
35 0 °C. 4'-Fluorophenyl(tolythio)methylisocyanide (4.86 g, 0.0189 mol - refer to Example 7 a) and 7 b) above) and 1.5.7-triazabicyclo[4.4.0.]dec-5-ene (2.63 g, 0.0189 mol) were mixed in CH₂Cl₂ and added dropwise to the cold reaction mixture. The reaction was kept

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cold for forty-eight hours. The solvent was evaporated and the crude mixture purified by flash chromatography (silica gel, CH₂Cl₂/methanol) to yield two products; an imidazole derivative [4-(4-Fluorophenyl)-5-(2-amino-4-pyrimidinyl)-pyrazole] and the title compound (550 mg). ¹H NMR δ 8.36 (d, 1H), 8.05 (s, 1H), 7.95 (m, 2H), 7.15 (m, 2H),
5 6.95 (d, 1H), 5.10 (s broad, 2H),

METHODS OF TREATMENT

The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of
10 any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cell, such as, but not limited to monocytes and/or macrophages.

Compounds of formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-8 and TNF
15 affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount
20 of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a specific embodiment the present invention provides for a method of treating inflammation in a mammal which method comprises administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Another specific
25 embodiment of the present invention provides for a method of treating stroke, asthma, ARDS, ischemia, and/or arthritis in a mammal which method comprises administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In particular, compounds of formula (I) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF
30 production by such mammal's cell, such as, but not limited to, monocytes and/or macrophages.

Accordingly, in another aspect, this invention relates to a method of inhibiting the
35 production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

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There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include arthritis, rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic β cells and Alzheimer's disease.

10 In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, such as osteoporosis, reperfusion injury, stroke, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Compounds of formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal, preferably a human, afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production.

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TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections.

Examples of such viruses include, but are not limited to, the lentivirus infections such as equine infectious anaemia virus, caprine arthritis virus, visna virus, or the maedi virus, or the retroviruses, such as feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus.

The compounds of formula (I) may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

Compounds of formula (I) have also been shown to inhibit the production of IL-8 (Interleukin-8, NAP). Accordingly, in a further aspect, this invention relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils into the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutrophil infiltration.

The compounds of formula (I) are administered in an amount sufficient to inhibit cytokine, in particular IL-1, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-8 or TNF; or (iii) the presence of IL-1, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-8 or TNF, respectively, is produced.

The discovery that the compounds of formula (I) are inhibitors of cytokines, specifically IL-1, IL-8 and TNF is based upon the effects of the compounds of formulas (I) on the production of the IL-1, IL-8 and TNF in *in vitro* assays which are described herein.

As used herein, the term "inhibiting the production of IL-1 (IL-8 or TNF)" refers to:

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a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

5 b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-8 or TNF) in a human to normal or sub-normal levels;

c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-8 or TNF) as a postranslational event; or

d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-8 or TNF) in a human to normal or sub-normal levels.

10 As used herein, the term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a
15 disease stated mediated by TNF.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a
20 monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples
25 of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor beta (TNF- β).

As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of formula (I) which will cause a decrease in
30 the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

As used herein, the cytokine referred to in the phrase "inhibition of a cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the
35 initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

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As TNF- β (also known as lymphotoxin) has close structural homology with TNF- α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- α and TNF- β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

In order to use a compound of formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of formula (I) may be administered in conventional dosage forms prepared by combining a compound of formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

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Compounds of formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100 °C. for half an hour. Alternatively, the

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solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of formula (I), the daily oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

35 BIOLOGICAL EXAMPLES

The cytokine-inhibiting effects of compounds of the present invention are determined by the following *in vitro* assays:

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Interleukin 1 (IL-1)

Human peripheral blood monocytes were isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta *et al.*, J Immunol, 132, 936 (1984). These monocytes (1×10^6) were
5 plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells were allowed to adhere for 2 hours, after which time non-adherent cells were removed by gentle washing. Test compounds were then added to the cells for 1h before the addition of lipopolysaccharide (50 ng/ml), and the cultures were incubated at 37°C for an additional
10 24h. At the end of this period, culture supernatants were removed and clarified of cells and all debris. Culture supernatants were then immediately assayed for IL-1 biological activity, either by the method of Simon *et al.*, J. Immunol. Methods, 84, 85, (1985) (based on ability of IL-1 to stimulate a Interleukin 2 producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore) or the method of Lee *et al.*, J. ImmunoTherapy, 6 (1), 1-12 (1990) (ELISA assay). Compounds of formula (I) as illustrated by Examples 1, 2, and 7 herein
15 were shown to be inhibitors of *in vitro* IL-1 produced by human monocytes.

Tumor Necrosis Factor (TNF)

Human peripheral blood monocytes are isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. *et al.*, J
20 Immunol, 132(2), 936 (1984). The monocytes are plated at a density of 1×10^6 cells/ml medium/well in 24-well multi-dishes. The cells are allowed to adhere for 1 hour after which time the supernatant is aspirated and fresh medium (1ml, RPMI-1640, Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum plus penicillin and streptomycin (10 units/ml) added. The cells are incubated for 45 minutes in the presence or
25 absence of a test compound at 1nM-10mM dose ranges (compounds were solubilized in dimethyl sulfoxide/ethanol, such that the final solvent concentration in the culture medium is 0.5% dimethyl sulfoxide/0.5% ethanol). Bacterial lipopoly-saccharide (*E. coli* 055:B5 [LPS] from Sigma Chemicals Co.) is then added (100 ng/ml in 10 ml phosphate buffered saline) and cultures incubated for 16-18 hours at 37°C in a 5% CO₂ incubator. At the end
30 of the incubation period, culture supernatants are removed from the cells, centrifuged at 3000 rpm to remove cell debris. The supernatant is then assayed for TNF activity using either a radio-immuno or an ELISA assay, as described in WO 92/10190 and by Becker *et al.*, J Immunol, 1991, 147, 4307.

Interleukin 8 (IL-8)

Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained in culture medium supplemented with 15% fetal bovine serum and 1%

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CS-HBGF consisting of aFGF and heparin. The cells are then diluted 20-fold before being plated (250 μ l) into gelating coated 96-well plates. Prior to use, culture medium is replaced with fresh medium (200 μ l). Buffer or test compound (25 μ l, at concentrations between 1 and 10 μ M) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO₂. At the end of the incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard curve. IC₅₀'s where appropriate are generated by non-linear regression analysis.

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Cytokine Specific Binding Protein Assay

A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay, the binding assay has been extensively validated to highly correlate with the results of the bioassay. A specific and reproducible binding assay was developed to test compounds belonging to the CSAID™ class of compounds using soluble cytosolic fraction from THP.1 cells and a radiolabeled compound. For instance, a suitable radiolabeled compound of the CSAID™ class of compounds is 4-(Fluorophenyl)-2-(4-hydroxyphenyl-3,5-t₂)-5-(4-pyridyl)imidazole which may be made in an analagous procedures as demonstrated in Adams et al., WO93/14081 or as illustrated below.

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In brief, the THP.1 cytosol was routinely prepared from cell lysate obtained by nitrogen cavitation followed by a 10 K x g low speed and a 100 K x g high speed centrifugation, the supernatant of which was designated as the cytosolic fraction. THP.1 cytosol was incubated with appropriately diluted radioligand at room temperature for a pre-determined time to allow the binding to achieve equilibrium. The sample was added to a G-10 column and eluted with 20 mM TRN, 50mM β -mercaptoethanol, NaN₃. The fraction encompassing the void volume was collected and the radioactivity was assessed by liquid scintillation counting. This was determined to reflect bound radioligand since the radioactive signal was abrogated by the presence of excess cold ligand in the incubation mixture or when there was no cytosolic fraction present. Compounds of Formula (I) at various doses were added to the binding assay to achieve inhibition of binding of the radiolabel. IC₅₀s as well as K_i values were determined by regression analysis and scatchard plot analysis respectively. There is generally excellent correlation between the IC₅₀ of compounds tested in both the binding assay and the bioassay and can

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be used interchangeably in many cases. Compounds of Formula (I) as illustrated by Examples 1 to 14 herein were shown to have activity in the CSBP assay.

5 Patent Application USSN 08/123,175 Lee et al., filed September 1993, whose disclosure is incorporated by reference herein in its entirety also describes the above noted method for screening drugs to identify compounds which interact with and bind to the CSBP. However, for purposes herein, the binding protein may be in isolated form in solution, or in immobilized form, or may be genetically engineered to be expressed on the surface of recombinant host cells such as in phage display system or as fusion proteins. Alternatively, whole cells or cytosolic fractions comprising the CSBP may be employed in the screening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein complex and compound capable of forming, enhancing or interfering with said complexes are detected.

15 More specifically, the Cytokine Specific Binding Assay is performed as follows:

MATERIALS:

Incubation buffer: 20 mM Tris, 1 mM MgCl₂, 20 mM Hepes, 0.02% NaN₃, store at 4°C. **Elution buffer:** 20 mM Tris, 50 mM 2-mercaptoethanol, NaN₃, store at 4°C.

20 **G-10 Sephadex:** add 100 g Sephadex G-10 (Pharmacia, Uppsala, Sweden) to 400 mL dd H₂O and allow to swell at room temperature for 2 hours. Decant fines and wash 3 times. Add NaN₃ and qs with dd H₂O to 500 mLs and store at 4°C.

Assemble Columns: Straw column, filter frit and tip (Kontes, SP 420160-000, 420162-002). Low sorb tubes (Nunc) used in binding reaction. THP.1 cytosol spun at 15000 rpm for 5 min to clarify. THP.1 cytosol prepared by hypotonic treatment of cells and lysis by decompression in nitrogen. Nuclei and membrane fragments removed by differential centrifugation (10,000 g for 1 hour and 100,000 g for 1 hour).

25 **Compounds:** Non-radioactive Compound I with corresponding EtOH control (dilutions made in incubation buffer) and ³H-Compound I (dilutions in incubation buffer).

30 **METHOD:**

A. Column Preparation

1) Begin 30 min before anticipated elution of reaction mixture; 2) Add 3 mL of G-10 slurry to column for bed vol of 1.5 ml; 3) Rinse with 7 mL elution buffer (fill to top of column); 4) Cut columns down to size.

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B. Sample Incubation

1) 15 min incubation at 4°C; 2) Binding reaction mixture; 100 µL cytosol, 10 µL cold Compound I or EtOH control, 10 µL ³H-Compound I (molar concentration depends on nature of study); 3) "Free" control = 100 µL incubation buffer in lieu of cytosol preparation.

5 C. Sample Elution

1) Elute at 4°C; 2) Add total reaction volume to G-10 column; 3) Add 400 µL elution buffer to column and discard eluate; 4) Add 500 µL elution buffer to column, collecting eluted volume in 20 ml scintillation vial; 5) Add 15 mL Ready Safe scintillation fluid; 6) Vortex and count in liquid scintillation counter for 5 minutes.

10 Include a "total input counts control" (10 µL of labeled ligand).

D. Data Analysis

1) Plot DPMS as output in graphic form and analyze by regression analysis and "Lundon ligand binding" software for the determination of IC₅₀ and K_d/K_i respectively; 2) Rank order the IC₅₀s of the tested compounds in the CSAIDbioassay and compare to that generated by the CSAID binding assay and establish a correlation curve.

The binding assay was further validated by the following criteria, i.e. THP.1 cytosol demonstrated saturable and specific binding of the radiolabeled compound.

20 **Preparation of 4-(Fluorophenyl)-2-(4-hydroxyphenyl-3,5-t₂)-5-(4-pyridyl)imidazole, (Compound I)**

A 2.9 mg (0.0059 mmol) portion of 2-(3,5-Dibromo-4-hydroxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, Compound I, was dissolved in 0.95 mL of dry DMF and 0.05 mL of triethylamine in a 2.4 mL round bottom flask equipped with a small magnetic stirring bar. A 1.7 mg portion of 5% Pd/C (Engelhard lot 28845) was added, and the flask was attached to the stainless steel tritium manifold. The mixture was degassed through four freeze-pump-thaw cycles, then tritium gas (5.3 Ci, 0.091 mmol) was introduced. The reaction mixture was allowed to warm to room temperature and was stirred vigorously for 20h. The mixture was frozen in liquid nitrogen, the remaining tritium gas (2.4 Ci) was removed, and the flask was removed from the manifold. The reaction mixture was transferred, using 3 x 1 mL of methanol as rinsings, into a 10 mL round bottom flask, and the solvents were removed by static vacuum transfer. A 1.5 mL portion of methanol was added to the residue, then removed by static vacuum transfer. The latter process was repeated. Finally, the residue was suspended in 1.5 mL of ethanol and filtered through a syringe-tip Millipore filter (0.45 micron), along with 3 x ca. 1 mL ethanol rinsings. The total filtrate volume was determined to be 3.9 mL, and the total radioactivity, 94.2 mCi. Solution was

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- determined to be 3.9 mL, and the total radioactivity, 94.2 mCi. HPLC analysis of filtrate (Partisil 5 ODS-3, 4.6 mm I.D. x 25 cm, 1 mL/min of 70:30:01 water/acetonitrile/trifluoroacetic acid, Radiomatic Flo-One Beta radio detector with 3 mL/min of Ecoscint-H cocktail through a 0.75 mL cell) showed the presence of
- 5 Compound I ($R_t = 60$ min. ca. 37% of total radioactivity), and a discrete intermediate presumed to be the monobromo derivative Compound Ia ($R_t = 11.8$ min, ca. 9%).

- The filtrate solution was evaporated to near dryness with a stream of nitrogen, and the residue was dissolved in about 1.2 mL of the HPLC mobile phase. The solution was separated by HPLC as shown below, and the peaks corresponding to Compounds I
- 10 and Ia and SB collected separately.

HPLC Method

Column	Altex Ultrasphere 10 mm I.D. x 25 cm
Mobile Phase	70:30:0.1 water/acetonitrile/trifluoroacetic acid
Flow Rate	5 mL/min
UV detection	210nm
Injection Volumes	0.05 - 0.4 mL
Retention Times	7.8 min Compound I 24 min Compound Ia

- The pooled Compound I fractions totaled 32 mL in volume and the radioactive concentration was 1.52 mCi/mL (total 48.6 mCi). The pooled SB Compound Ia [^3H] fractions (totaling 10.1 mCi) were evaporated to dryness and the residue was transferred
- 15 quantitatively into a glass vial using 3.8 mL of absolute ethanol for further analysis.

- An 8 mL (12.2 mCi) portion of Compound I was evaporated to dryness *in vacuo* at $<35^\circ\text{C}$, then redissolved in 0.5 mL of mobile phase. The whole volume was injected into the HPLC system described above, and the appropriate peak was collected. Evaporation of the collected eluate *in vacuo* at $<35^\circ\text{C}$ and transfer of the yellow residue
- 20 into a vial with absolute ethanol provided a solution (3.8 mL, 2.44 mCi/mL) of Compound I. The portion of this solution used for NMR analyses was first evaporated to dryness using stream of nitrogen then taken up in CD_3OD .

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Analysis of 4-(4-Fluorophenyl)-2-(4-hydroxyphenyl-3,5-t₂)-5-(4-pyridyl)imidazole, Compound I.
Radiochemical Purity by HPLC

Method

Column	Ultrasphere Octyl, 5mm, 4.6 mm I.D. x 25 cm, Beckman
Mobile Phase	350:150:0.5(v/v/v) water/acetonitrile/trifluoroacetic acid
Flow Rate	1.0 mL/min
Mass detection	UV at 210 nm
Radioactivity detection	Ramona-D radioactivity flow detector
Scintillator	Tru-Count (Tru-Lab Supply Co.)
Flow rate	5.0 mL/min
Cell volume	0.75 mL
Retention time	7.7 min

Result98.7Radioactive Concentration by Scintillation CountingMethod

Scintillator	Ready Safe (Beckman Instruments, Inc.)
Instrument	TM Analytic model 6881
Efficiency	Automated DPM calculation from quench curve

Result

2.44 mCi/mL

Specific Activity by Mass SpectrometryMethodCI-MS, NH₃ reagent gasResult

20.0 Ci/mmol

³H Distribution:

Unlabeled	44%
Single Label	43%
Double Label	13%

³H NMR⁹Method

Instrument	Brunker AM 400
Experiment	Proton decoupled ³ H NMR Proton non-decoupled ³ H NMR Proton non-decoupled ³ H NMR
Peak Referencing	Solvent Peak of methanol δ 3.3
Solvent	Methanol-d ₄
<u>Result</u>	Tritium is incorporated exclusively on the carbon atoms ortho to aromatic hydroxyl group

Analytical Summary

<u>Assay</u>	<u>Result</u>
Radiochemical purity determined by HPLC	98.7%
Radioactivity concentration determined by scintillation counting	2.44 mCi/mL
Specific activity determined by mass spectrometry	20.0 Ci/mmol
³ H NMR	agrees with the proposed structure

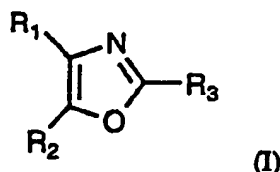
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The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

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What is claimed is:

1. A compound of the formula:



wherein:

R₁ and R₂ are independently selected from an optionally substituted aryl or heteroaryl group, provided that at least one of R₁ and R₂ is an optionally substituted heteroaryl, and further provided that both R₁ and R₂ are not the same heteroaryl group;

wherein when one of R₁ and R₂ is an optionally substituted aryl ring, the ring is substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, -C(Z)NR₇R₁₇, -C(Z)OR₂₃, -(CR₁₀R₂₀)_m COR₃₆, -SR₅, -SOR₅, -OR₃₆, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃, or -(CR₁₀R₂₀)_mNR₁₀R₂₀;

and which, for other positions of substitution, is halo, -(CR₁₀R₂₀)_m-cyano, -C(Z)NR₁₆R₂₆, -C(Z)OR₈, -(CR₁₀R₂₀)_m COR₈, -(CR₁₀R₂₀)_mS(O)_mR₈, -(CR₁₀R₂₀)_mOR₈, halo-substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_mNR₁₀C(Z)R₈, -(CR₁₀R₂₀)_mNR₁₀S(O)_mR₁₁, -(CR₁₀R₂₀)_mNR₁₀S(O)_mNR₇R₁₇, -(CR₁₀R₂₀)_mZC(Z)R₈ or -(CR₁₀R₂₀)_mNR₁₆R₂₆;

and when one of R₁ and R₂ is an optionally substituted heteroaryl group, the substituent groups include one or two substituents each of which is independently selected from C₁₋₄ alkyl, halo, C₁₋₄ alkoxy, C₁₋₄ alkylthio, NR₁₀R₂₀, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₂₂;

R₃ is -X_aP(Z)(X_bR₁₃)₂, X_c or -(CR₁₀R₂₀)_n R₄;

R₄ is Q-(Y₁)_t;

Q is an aryl or heteroaryl group;

X_c is hydrogen, -(CR₁₀R₂₀)_n (Y₂)_p, -(CR₁₀R₂₀)_n-C=C-(CR₁₀R₂₀)_n(Y₂)_p, -(CR₁₀R₂₀)_n-C≡C-(CR₁₀R₂₀)_n(Y₂)_p, or halosubstituted C₁₋₁₀ alkyl;

t is an integer having a value of 1 to 3;

p is 0 or an integer having a value of 1, provided that when p is 0 then Y₂ is hydrogen;

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- X_a is -NR₈-, -O-, -S- or a C₁₋₁₀ alkylene chain optionally substituted by C₁₋₄ alkyl and optionally interrupted by -NR₈-, -O- or -S-;
- X_b is independently selected from -(CR₁₀R₂₀)_n-, -NR₈-, -O- or -S-;
- Z is oxygen or sulfur;
- 5 n is 0 or an integer having a value of 1 to 10;
 n' is an integer having a value of 1 to 10;
 m is 0, or the integer 1 or 2;
 m' is 1 or 2;
 m'' is 0 or an integer having a value of 1 to 5;
- 10 Y_1 is independently selected from hydrogen, C₁₋₅ alkyl, halo-substituted C₁₋₅ alkyl, halogen, -X_a-P(Z)-(X_bR₁₃)₂ or -(CR₁₀R₂₀)_nY₂;
 Y_2 is halogen, -OR₈, -NO₂, -S(O)_m'R₁₁, -SR₈, -S(O)_m'NR₈R₉, -NR₈R₉, -O(CR₁₀R₂₀)_n'NR₈R₉, -C(O)R₈, -CO₂R₈, -CO₂(CR₁₀R₂₀)_n' CONR₈R₉, -ZC(O)R₈, -CN, -C(Z)NR₈R₉, -NR₁₀C(Z)R₈, -C(Z)NR₈OR₉, -NR₁₀C(Z)NR₈R₉,
 15 -NR₁₀S(O)_m'R₁₁, -N(OR₂₁)C(Z)NR₈R₉, -N(OR₂₁)C(Z)R₈, -C(=NOR₂₁)R₈, -NR₁₀C(=NR₁₅)SR₁₁, -NR₁₀C(=NR₁₅)NR₈R₉, -NR₁₀C(=CR₁₄R₂₄)SR₁₁, -NR₁₀C(=CR₁₄R₂₄)NR₈R₉, -NR₁₀C(O)C(O)NR₈R₉, -NR₁₀C(O)C(O)OR₁₀, -C(=NR₁₃)NR₈R₉, -C(=NOR₁₃)NR₈R₉, -C(=NR₁₃)ZR₁₁, -OC(Z)NR₈R₉, -NR₁₀S(O)₂CF₃, -NR₁₀C(Z)OR₁₀, 5-(R₁₈)-1,2,4-oxadiazol-3-yl or 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl;
- 20 R_5 is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the moieties -SR₅ being -SNR₇R₁₇ and -SOR₅ being -SOH;
 R_6 is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or C₃₋₅ cycloalkyl;
- 25 R_7 and R_{17} is each independently selected from hydrogen or C₁₋₄ alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₂₂;
- R_8 is hydrogen, heterocyclyl, heterocyclalkyl or R₁₁;
- 30 R_9 is hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R_8 and R_9 may together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂;
- 35 R_{10} and R_{20} is each independently selected from hydrogen or C₁₋₄ alkyl;
 R_{11} is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

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- R₁₂ is hydrogen, -C(Z)R₁₃ or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;
R₁₃ is hydrogen, C₁₋₁₀ alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;
- 5 R₁₄ and R₂₄ is each independently selected from hydrogen, alkyl, nitro or cyano;
R₁₅ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;
R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members
10 which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂ ;
R₁₈ and R₁₉ is each independently selected from hydrogen, C₁₋₄ alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together R₁₈ and R₁₉ denote a oxygen or sulfur;
- 15 R₂₁ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C₁₋₁₀ alkanoyl;
R₂₂ is R₁₀ or C(Z)-C₁₋₄ alkyl;
R₂₃ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;
R₃₆ is hydrogen or R₂₃;
20 or a pharmaceutically acceptable salt thereof.
2. The compound according to Claim 1 wherein R₁ or R₂ is an optionally substituted 4-pyridyl or 4-pyrimidinyl.
- 25 3. The compound according to Claim 2 wherein the optional substituent is C₁₋₄ alkyl or NR₁₀R₂₀.
4. The compound according to any of Claims 1 to 3 wherein R₁ or R₂ is an optionally substituted phenyl.
- 30 5. The compound according to Claim 4 wherein the one or more optional substituents are independently selected from halogen or methoxy.
6. The compound according to any of Claims 1 to 5 wherein R₃ is X_C or
35 -(CR₁₀R₂₀)_nR₄.

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7. The compound according to Claim 6 wherein R₃ is hydrogen, -(CR₁₀R₂₀)_n(Y₂)_p, -(CR₁₀R₂₀)_n CH₃; and Y₂ is -NR₈R₉ or -NR₁₀C(Z)R₈; and R₄ is an optionally substituted phenyl.
- 5 8. The compound according to Claim 5 or 6 wherein R₃ is hydrogen, methyl, amino, -NR₁₀C(O)R₈, phenyl, or phenyl substituted by -SR₈ or -S(O)_mR₁₁.
9. The compound according to Claim 1 which is:
- 10 5-(3-Methoxyphenyl)-2-methyl-4-(4-pyridyl)oxazole;
5-(4-Fluorophenyl)-2-methyl-4-(4-pyridyl)oxazole;
2-Methyl-4-(Phenyl)-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-2-methyl-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-2-phenyl-5-(4-pyridyl)oxazole;
2-Amino-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole.
- 15 4-(4-Fluorophenyl)-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-5-(2-methylpyrid-4-yl)oxazole;
4-(3,4-Dichlorophenyl)-5-(4-pyridyl)oxazole;
4-(3-Chlorophenyl)-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)oxazole;
- 20 4-(4-Fluorophenyl)-2-[4-(methylsulfinyl)phenyl]-5-(4-pyridyl)oxazole;
2-Acetamido-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-5-(2-amino-pyrimidin-4-yl)oxazole; or pharmaceutically acceptable salts thereof.
- 25 10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound according to any of Claims 1 to 9.
11. A method of treating a cytokine mediated disease in an animal in need thereof which method comprises administering to said animal an effective cytokine mediating
- 30 amount of a compound according to any of Claims 1 to 9.
12. The method according to Claim 11 wherein the cytokine mediated disease is asthma, adult respiratory distress syndrome, stroke, bone reabsorption diseases, arthritic joint conditions, and other inflammatory diseases.
- 35 13. The method according to Claim 11 or 12 wherein the compound is 5-(3-Methoxyphenyl)-2-methyl-4-(4-pyridyl)oxazole;

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- 5-(4-Fluorophenyl)-2-methyl-4-(4-pyridyl)oxazole;
2-Methyl-4-(Phenyl)-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-2-methyl-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-2-phenyl-5-(4-pyridyl)oxazole;
5 2-Amino-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-5-(2-methylpyrid-4-yl)oxazole;
4-(3,4-Dichlorophenyl)-5-(4-pyridyl)oxazole;
4-(3-Chlorophenyl)-5-(4-pyridyl)oxazole;
10 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-2-[4-(methylsulfinyl)phenyl]-5-(4-pyridyl)oxazole;
2-Acetamido-4-(4-fluorophenyl)-5-(4-pyridyl)oxazole;
4-(4-Fluorophenyl)-5-(2-amino-pyrimidin-4-yl)oxazole; or pharmaceutically acceptable
salts thereof.
15
14. The method according to any of Claims 11 to 13 wherein the mediation of the
disease state is by Interleukin-1 (IL-1).
15. The method according to any of Claims 11 to 13 wherein the mediation of the
20 disease state is by Tumor Necrosis Factor (TNF).
16. A method of treating inflammation in a mammal in need thereof which comprises
administering to said mammal an effective amount of a compound according to any of
Claims 1 to 9.

RECTIFIED SHEET

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13067

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/44,31/505 ; C07D 413/04

US CL : 546/275; 544/331,333; 514/340,275,272,269,256

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/331,333 ;514/275,272,269,256,340; 546/275

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS,CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, volume 99, no.21, issued 21 November 1983, Sallmann, "Trisubstituted oxazo compounds" see abstract no. 175755w, WO 83/02,613 (04.08.83).	1-17
X	Chemical Abstracts, volume 99, no.3, issued 18 July 1983, Sallmann, "Diaryloxazole compounds" see abstract no. 22451u, S. African ZA 82/00,932 (12.2.82).	1-17
X	Chemical Abstracts, volume 97, no. 1, issued 05 July 1982, Sallmann, "Trisubstituted imidazole derivatives: pharmaceutical compositions containing them and their use," see abstract no. 6298c, EP 45,081 (03.02.82).	1-17

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*g*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 JANUARY 1995	Date of mailing of the international search report 06 FEB 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JANE FAN Telephone No. (703) 308-4705

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13067

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, volume 97, no.11, issued 13 September 1982, Sallmann, "Diarylmidazole compounds, pharmaceutical drugs containing them, and their use", see abstract no. 92274w, EP 46,451 (24.02.82).	1-17
X	Chemical Abstracts, volume 100, no.1 issued 02 January 1984, Sallmann, "Trisubstituted oxazoles", see abstract no. 6496w, EP 84,756(03.08.83).	1-17
X	Chemical Abstract, volume 83, no 15 issued 13 October, 1975, Fitzi, "Imidazole derivatives" see abstract no. 131598n, Swiss 561,718 (15.05.75).	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13067

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-10(in part) of groups I, II and for asthma in claims 11-17
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13067

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

I. Claims 1-10 wherein one of R1,R2 is pyridyl, the other R1,R2 and all other variables contain no additional hetero-ring.

II. Claims 1-10 wherein one of R1,R2 is pyrimidyl, the other R1,R2 and all other variables contain no additional hetero-ring.

III. Claims 1,4-8,10 wherein both R1,R2 contain pyridyl, other variables contain no additional hetero-ring.

IV. Claims 1,4-8, 10 wherein both R1, R2 contain pyrimidyl, other variables contain no additional hetero-ring.

V. Claims 1,4-8,10 wherein either or both R1,,R2 contain a hetero-ring other than pyridyl or pyrimidyl, each hetero ring or any combination of them is distinct. (Since the claimed language is indefinite, the exact meaning and scope can not be ascertained.) No additional hetero-ring anywhere in the formula.

VI. Claims 1,4-8, 10 wherein one or both R1, R2 contain hetero-ring other than pyridyl or pyrimidyl, each or combination thereof is distinct. (Other variables contain hetero-ring since the claimed language is indefinite. The exact meaning can not be ascertained.)

A method of use in claims 11-17 be considered together with any of the above group elected.

The above groups lack unity of invention because the five-membered oxazole ring would not have been of sufficient similarity (common core structure) to allow a Markush grouping exhibiting unity. Note oxazole ring containing compounds exhibit a variety of uses such as sun screens.